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Long-term morbidity and mortality following bloodstream infection: A systematic literature review

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Abstract

Objectives: Bloodstream infection results in significant short-term morbidity and mortality. No literature review has studied the long-term outcome following a bloodstream infection. This PROSPERO registered systematic review evaluated studies, which measured the association of a bloodstream infection with long-term morbidity and mortality.

Methods: Databases were systematically searched for studies of adult patients reporting morbidity and/or mortality one year or more following a bloodstream infection in comparison to a matched cohort without a bloodstream infection.

Results: Ten observational studies were included in the final analysis. Five studies assessed only mortality, two assessed morbidity and mortality and three studies assessed morbidity only. The one year mortality ranged from between 8 and 48% for patients with bloodstream infection. The pooled risk ratio of death at one year was significantly higher for patients with bloodstream infection when compared to the matched cohort (RR 4.04 [95% CI 1.84-8.87]).

Conclusions: Bloodstream infection was associated with poor long-term outcome measured at one year when compared to matched controls. More evidence is needed to determine if this association is causative.

Keywords: bacteraemia, septicaemia, bloodstream infection, long term, outcome, endpoint, mortality.

Introduction

Bloodstream infections (BSI) are a significant cause of morbidity and mortality worldwide (1). The practice of measuring mortality at one month following a BSI is well established (2,3). A recent review of clinical trials of antibiotics for patients with bloodstream infection in the last 10 years demonstrated all outcomes were measured at 90 days or less (4).

BSI have been associated with high long-term mortality, subsequent cardiovascular disease (5–7) and increased risk of recurrent bloodstream infection (8). The interpretation of the impact of BSI in many of these studies is limited by the absence of a suitable comparator group (5–7). The measurement of outcome following a serious infection beyond the short term is potentially confounded by co-morbid disease as BSI often occurs in patients with pre-disposing disorders, which carry a high risk of increased morbidity and premature death when compared to the general population. Risk factors that have been associated with acquisition of a bloodstream infection include: diabetes, HIV infection, chronic liver disease, previous and repeated hospitalisation, corticosteroid therapy use, chronic renal failure, presence of a solid tumour and overall degree of co-morbid disease (9).

The long-term sequelae from other serious infections have been well described (10). Sepsis has been evaluated in multiple studies using outcome measurements such as: quality of life adjusted years, subsequent cardiovascular risk and mortality beyond one year (11). Patients with sepsis have ongoing mortality beyond the usual short-term outcome time point with survivors consistently demonstrating impaired quality of life (11).

Understanding the long-term impact of a BSI on mortality and morbidity is important to adequately establish disease burden, define when to measure endpoints for clinical trials and to guide allocation of healthcare and research resources.

The objectives of this systematic review were to i) identify studies that assessed the outcome (either morbidity or mortality) following a bloodstream infection at one year or greater ii) where morbidity was assessed, describe the methods used to assess and describe associated morbidities, iii) include studies which included a matched cohort of patients without bloodstream infection as a comparator.

Methods

This study has been reported in accordance with the PRISMA guidelines on reporting systematic reviews (12) and was registered with the PROSPERO international prospective register of systematic reviews (PROSPERO 2016:CRD42016052052) on 8th December 2016, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016052052.

We searched the following electronic bibliographic databases: EMBASE, PubMed, The Cochrane Library, Scopus and references from included articles. The search strategy included terms relating to bloodstream infection and describing an outcome in terms of morbidity or mortality. The search protocol was developed in consultation with a specialist medical librarian. The terms used were (bloodstream infection OR bacteraemia OR septicaemia) AND (cohort OR follow up OR longitudinal OR prospective OR retrospective studies) NOT (paediatric OR child OR neonate OR perinatal OR baby OR toddler). Studies reviewed were restricted to English and studies exclusively of paediatric patients were excluded. Reviews, case reports and small case series were excluded (<10 total number of patients). Studies were excluded if there was no case match or case control with a patient without bloodstream infection. Studies assessing patients with sepsis without a large proportion of bloodstream infections (>80%) were also excluded. There were no exclusions based on the date of the study. The searches were re-run prior to the final analyses.

The PECO criteria used to select studies were as follows:

- Patient population/problem: adult patients
- Exposure: bloodstream infection
- Comparator: adult patients without bloodstream infection
- Outcome: morbidity or mortality at or beyond 1 year

Data Extraction and management

The authors JFM and ER independently screened search results according to the PECO criteria. Details of each study were extracted and results tabulated. Patient demographics, organisms cultured, nature of matching and ratio, and outcome measurements were extracted from the original publications.

Outcome measures and definitions

The time to follow up must have occurred at one year or beyond. Reasonable measures to exclude common bloodstream contaminants were assessed. Mortality was the primary endpoint. Morbidity measures were included if validated criteria were used as a definition of condition or event.

Data analysis

Analyses were performed in the statistical program R (13) with the Metafor statistical software package (14), and Graphpad prism version 7 (15). Studies comparing mortality and exposure to bloodstream infection were included in the pooled analysis. Unadjusted mortality was compared between the two cohorts (BSI and non-BSI) at one year. Due to variation in organism and host across the different studies heterogeneity was expected and results were combined with a random effects model (16) . Heterogeneity between studies was evaluated using the Q statistic ($p < 0.01$ significant heterogeneity) and I^2 tests (>56% likely high heterogeneity) (17). Cumulative difference in unadjusted mortality and associated risk ratios between the BSI and non BSI cohorts at each reported time interval up to one year were plotted as an assessment of the rate of change over time in mortality between the two cohorts. Unadjusted relative risk of death and 95% confidence interval was calculated for each time point based on published rates of mortality in each study.

Results

Study Characteristics

The search strategy identified 10,135 citations using the described search strategy as shown in figure 1. Two hundred and forty-one abstracts and 39 full-text publications were chosen for full review. Ten studies met our inclusion criteria. Six studies were multicentre studies and four were single centre studies. Study characteristics as shown in table 2. There were no international multicentre matched studies of long term outcome following a bloodstream infection. JFM and HW completed assessment of the selected studies utilising the Newcastle-Ottawa Quality Assessment Scale to

determine the quality of the study relative to our question of interest as described in table 1. There were no randomised clinical trials for BSI that used outcome measures at one year or beyond.

Mortality

Long term follow-up for mortality was reported in seven of the ten studies with the duration of follow-up ranging from 1 to 12 years (18–24). Mortality was measured at variable intervals within the follow-up period with one month the most commonly reported mortality time point other than one year (19–21,24).

The seven studies which assessed mortality evaluated this outcome in comparison to matched controls, which were non-BSI hospital controls in four studies and population controls in the other three. All studies with the exception of one (25) included adjustments for co-morbid disease with this most commonly measured as a Charlson index or score(26). Variation in mortality was seen in the matched group dependent upon the case selection method. Mortality in the three studies using non-BSI patients as controls was (BSI vs non-BSI) 48% vs. 27% (23), 60% vs. 6% (22)and 29.7 vs. 23.9% (24). Studies reporting mortality in comparison to population controls (BSI vs population control) describe mortality of 44.6% vs 4.1% (18), 41.4% vs 2.6% (27)and 8% vs 3.9%(28). Pooled random effects model of mortality at one year is shown in figure 2. The pooled risk ratio of death for patients with BSI of was 4.04 (95% Confidence interval 1.84 – 8.87) when compared to the non-BSI cohort. There was a high degree of heterogeneity amongst the included studies as shown in the funnel plot in appendix 1 (Q statistic $p = <0.001$ and I^2 99.88%).

The plot of cumulative difference in mortality demonstrated a divergent mortality over time between the BSI and non-BSI cohorts as shown in figure 3. Table 3 describes a significant increase in relative risk of death in patients with BSI in all but one study.

Studies that utilised hospitalised patients as the matched cohort had an odds ratio of mortality of 1.99 (95% CI 1.87, 2.11), in contrast studies using a general population matched cohort had a statistically significant ($p <0.0001$) odds ratio of 18.92 (95% CI 18.40, 19.47).

Cause of death

Reference to the cause of death was made in three of the seven studies reporting mortality (18,23,25,27).

Leibovici and colleagues (23) reported on bacterial infection as a cause of death within the first and second month post bloodstream infection. Attributed cause of death due to infection in the BSI group declined over the first two months of follow-up (21 and 12% respectively). In the matched group the reported rate of death from infection over the same period was 2 and 7% respectively. Cause of death in the longer term was not assessed in this study.

Nielsen and colleagues (27) reported within the first year, cancer and cardiovascular disease were the most common causes of death in patients with bloodstream infection. The most common causes of death were cancer and cardiovascular disease (54%) in patients with BSI who survived beyond one year. Gotland and colleagues study of *S.aureus* showed cancer as the overall leading cause of death accounting for 1 in 4 deaths (18).

Morbidity

Standardised morbidity measures were reported in five of the studies identified (20,24,29–31)(Table 4). Risk of functional decline and quality of life was significant amongst BSI patients at 3 months post index event as measured with the Barthel-20 (aRR 5.1 95% CI 1.2-22.3) and EQ-5D-3L (aRR 1.3 95% CI 0.8-2.1) respectively(29). These differences were less at 1 year for functional status (aRR 1.6 CI 0.5-4.5) and remained the same for quality of life (aRR 1.3 CI 0.8-1.2) (32). This study included 71 patients with first time community acquired bloodstream infection and compared them to 71 hospitalised, blood culture negative patients.

Higher rates of sick leave utilisation were identified in patients with bloodstream infection (aRR 1.51; CI 1.34 to1.70) (20). Rates of venous thromboembolism were increased amongst a population study of patients with *Staphylococcus aureus* bloodstream infection (31). This increase in incidence was seen in a population study of community acquired bloodstream infection with a collection of different pathogens at 90 days but did not remain significant at one year (24).

There was no significant differences in the rates of myocardial infarction or stroke amongst bloodstream infection patients when compared to culture-negative controls (21).

Discussion

This systematic review identified ten studies that measured long-term mortality or morbidity as an outcome following a bloodstream infection in comparison to a non-BSI cohort. These were all observational studies, which included different pathogens and included community, health-care associated and hospital acquired infections. Some heterogeneity was

expected as studies of this type define different criteria for the included pathogen, the selection of the matched population and the degree and measurement of comorbidity. All studies with the exception of one (25) have attempted to account for age, hospitalisation, co-morbid disease states by matching and adjustments in analysis. A significant increase in mortality was seen in six of the seven studies when measured at one year.

The degree of mortality varied considerably ranging from 18 to 60% mortality in the BSI and 2.6 to 27% in the non-BSI group at one year across the seven studies reporting mortality. The highest mortalities were seen in a study of liver transplant patients (60%), a study of exclusively *Staphylococcus aureus* BSI (44.6%) and in the oldest study in the group (48%) (18,23,33) . A high co-morbidity cohort – liver transplant, virulence of the selected pathogen (*S. aureus*) and high baseline mortality (27% in non-BSI cohort) may account for the higher mortality seen in these studies. Conversely the lowest mortality was seen in a study of patients selected for being part of the workforce immediately prior to acquiring their BSI which resulted in a lower overall age of the cohort (20 to 58 years) and perhaps lesser degree of co-morbidity and frailty which might have contributed to the lower mortality (34) . The nature of the matched population had a large impact on the odds ratio of death. There was a large reduction in the odds ratio of death when comparing hospital versus population matched studies. The odds ratio of death was significantly different (10 fold less) when population matched cohort studies were compared to hospital matched studies (OR 18.92 to OR 1.99 respectively). Further interrogation of potential moderators of the mortality outcome was limited by the small number of studies that have attempted to address this question.

Studies that measured short-term mortality suggest a slowing in the rate of divergence of mortality between BSI and non-BSI beyond ninety days as evidenced by a flattening in the gradient seen in figure 2. Whilst the greatest degree of mortality likely occurs early (<90 days) mortality continues to diverge in many of the studies beyond this point. The two studies that reported the second and third greatest divergence in mortality over the one year period compared BSI to non-BSI from population controls rather than hospital controls (35,36) (Figure 2).

The difficulty in assessing long-term outcome is extricating the impact the bloodstream infection has on mortality from the patient type who is at risk of acquiring a bloodstream infection. Patients at risk of bloodstream infection are those who experience multiple hospitalisations and have multiple co-morbidities (9). All studies with the exception of one,

included adjustment for confounding. However the potential for residual and unmeasured confounding would be seen as highly probable.

Three studies reported cause of death with different methodology limiting their comparability (35–37). One study only described infection as the attributable cause, which was higher in the bloodstream infection group but was not specifically measured in the longer term (37). Two studies reported cause of mortality in comparison to population controls, one study categorised cause of death to attributable organ system and the second by disease state (35,36). The differential results, reflects different temporal analysis, variance in patient cohort and/or different causative pathogens (first time community acquired bacteraemia versus *S. aureus* bacteraemia).

Standardised morbidity outcomes also demonstrated some association with poorer outcome for patients with bloodstream infection with some measures. There were two studies, which assessed functional outcomes via different measures. A small prospectively matched cohort of 71 patients with bloodstream infection assessed function and quality of life via the validated tools Barthel-20 (38) and EQ-5D (39) whilst the other employed the endpoints of sick leave utilisation and disability. A differential deterioration in function was apparent at 3 months though less so at 12 months when compared to the matched cohort no difference in QOL measures was demonstrated. Increased sick leave utilisation also occurred in patients with bloodstream infection.

The associated incidence of co-morbid disease was assessed by measurement of venous thromboembolism by two studies and by myocardial infarction and stroke in one study. Both of the studies examining the occurrence of venous thromboembolism demonstrated an association with bloodstream infection though the effect appears to occur within the first 90 days post infection with limited association at 1 year. The studies assessed different groups of pathogens (*S. aureus* and community acquired bloodstream infection) and the subsequent occurrence of venous thromboembolism though they differed in the matched cohort. Mejer (31) utilised population controls and Dalager-Pedersen (40) used hospitalised controls which may account for the differences in findings. The association of venous thromboembolism has been previously described in patients with acute infectious diseases and sepsis (41).

There is a large body of evidence describing the consequences of severe infections extend beyond the first month (10). Studies assessing long term outcomes following sepsis have also demonstrated poor outcomes in terms of morbidity and mortality. These studies demonstrated increased mortality beyond the traditional outcome measure time points. Quality

of life and functional status have also been shown to be poorer in survivors of sepsis (42–45). The poor long-term outcome in sepsis was proposed to be due to one of three possible explanations. 1. Sepsis usually happens in the elderly and sick, and it causes deterioration in the life expectancy a functional status as an acute non-specific event. 2. An interaction exists between specific mechanisms of sepsis and underlying disorders. 3. Long-term consequences directly relate to the infection (10). Explanations 2 and 3 may be influenced by the acute management of the disease and may subsequently influence the long-term outcome of the individual (10). The observed long-term risk of cardiovascular events (46), and vulnerability to subsequent infection have been associated with increased long term morbidity and mortality in sepsis cohorts (47). Endovascular inflammation and ongoing risk of infection could result in an interaction between acute infective episode, underlying disease state and long-term outcome.

Whilst there is overlap with sepsis, a bloodstream infection is not necessarily synonymous with sepsis. A prospective multi-centre survey of 23 hospitals in France identified only 39.9% of patients with bloodstream infection with severe septic or septic shock according to sepsis 2 guideline criteria (48,49).

In conclusion, this systematic review highlights an association between bloodstream infection and poor long-term patient outcomes. The heterogenous nature of the included studies and the small number of studies result in an insufficient body of evidence to consider the association a causal interaction.

Study design for understanding the long-term impact of BSI could be better informed by combining positive design elements of the studies assessed in this review. Large scale studies matched for age and gender with adjustments for co-morbidity and collection of date of death to allow high resolution comparative adjusted survival curves would provide valuable information as to the most relevant time to measure mortality following a bloodstream infection. Assessment of cause of death and associated subsequent disease states such as cardiovascular events and infection would be valuable in the formulation of a testable hypothesis of pathophysiological interaction between BSI and associated co-morbidity and long-term outcome. Measurement of morbidity would ideally incorporate a standardised measurement of functional or performance and quality of life. The application of these tools to large scale population studies would be impractical and would be better assessed in small scale studies then correlated to measurements more applicable to large scale data capture such as hospital re-admission rate, utilisation of sick leave or timing of return to

work. This would provide some validation of surrogate markers of function and quality of life for use in large-scale population studies.

Understanding when to measure survival to reflect the true burden of mortality and how accurately reflect functional outcomes would provide useful metrics for measurement of outcomes in clinical trials of severe infections that would be highly relevant to patients and clinicians at the bedside.

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Conflict of Interest Disclosure

The authors declare no conflicts of interest

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228.

Table 1. Study Quality Assessment using the Newcastle Ottawa Scale.

Study	**Selection**	**Comparability**	**Outcome**
Tauriainen 2017	****	*	***
Dalager-Pedersen 2016	****	*	**
Gotland 2016	****	*	***
Nielsen 2015	****	*	***
Dalager-Pedersen 2014a	***	*	***
Dalager-Pedersen 2014b	****	*	***
Mejer 2014	****	*	***
Karvellas 2011	****	*	***
Leibovici 1995	****	**	***

Table 2. Characteristics of studies reporting long-term outcomes in patients with bloodstream infection.

First Author/ year	Study design, period, region	N/ Ratio	Population characteristics	Case matching	Co-Morbid state	Adjustments	Duration of follow up	Outcome
Tauriainen 2017	Retrospective comparison of BSI and non-BSI patients post coronary surgery, 2006 to 2013, Single centre in Finland	27 (>1:10)	Adult patients undergoing isolated coronary artery bypass grafting with a BSI identified post operatively	Comparison to blood culture negative patients and all other post coronary surgery cases	Yes	No adjustments	5 years	Mortality at 30 days, 1 and 5 years
Dalager-Pedersen 2016	Prospective case matched study in adults, 2011-2014, Single site 800 bed community hospital, North Denmark	71 (1:1)	≥18 years Hospital admission with first episode community acquired bloodstream infection	Negative blood culture, age (18-59, 60-79, 80+), gender, duration since blood culture draw +/- 2 days	Yes	Age, gender and comorbidity	1 year	Functional status EQ-5D, Barthel
Gotland 2016	Prospective matched cohort, 1992-2014, Nationwide register in Holland	25,855 (1:10)	Registry of consecutive Staphylococcus aureus bloodstream infection	Negative blood culture, Age and gender	Yes	Charlson Comorbidity index, age, gender and time period	5 years	Mortality at 1 and 5 years
Nielsen 2015	Retrospective population based cohort study, 2000-2008, Funen County Denmark	7783 (1:5)	First time bloodstream infection >14 years of age	Population controls Absence of bloodstream infection, gender, year of birth and residency in Funen County	Yes	Martial status, Charlson comorbidity classification 0,1,2,>=3 and a history of alcohol dependence	12 years	Mortality at 30 and 90 days, and 1 year
Dalager-Pedersen 2014a	Prospective case matched study, 1996 to 2011, North Denmark	450 (1:10)	Nationwide study, 20-58 years of age who were part of the workforce in the 4 weeks prior to admission. No	Blood culture negative controls	Yes	Age (continuous), gender and presence of comorbidity (binary). Subgroup analysis by pre-existing disease, COPD, recent antibiotic	1 year	Mortality at 30 days and 1 year Return to work, utilisation of sick leave, disability pension.

			documented bloodstream infection in the previous year.1996 to 2011, Northern Denmark			use, LRTI and UTI.		
Dalager-Pedersen 2014b	Retrospective analysis of population databases from Northern Denmark 1992-2011.	4213 (1:5) (1:10)	Community acquired BSI, hospital admissions ≥15 years of age, 1992 to 2011, Northern Denmark	Matched non-BSI hospital admission. Matched population controls	Yes	Age, marital status, previous AMI, previous cerebrovascular disease, diabetes, COPD, other cardiovascular disease, other comorbid disease and the use of medications for cardiovascular disease	1 year	Myocardial infarction and stroke
Dalager-Pedersen 2014c	Retrospective analysis of population databases from Northern Denmark 1992-2011.	4389 (1:5) (1:10)	Community acquired BSI, hospital admissions ≥15 years of age	Matched non-BSI hospital admission. Matched population controls	Yes	Age, gender, cancer, cardiovascular diseases, diabetes, obesity, COPD, renal disease and recent hospital contact	1 year	Mortality at 90 days and 1 year Venous thromboembolism
Mejer 2014	Nationwide register based retrospective matched cohort study, 1995-2008, Denmark	15,669 (1:10)	All registered cases of SAB within the Danish population >15 years of age during the study period	Absence of bloodstream infection, age and gender	Yes	Previous venous thromboembolism, intravenous drug use, cocaine abuse	1 year	Venous thromboembolism incidence
Karvellas 2011	Retrospective cohort from single centre in the United Kingdom	15 (1:13)	≥17 years post liver transplant	Absence of a bloodstream infection in a post liver transplant patient	Yes	APACHE II score	5 years	Mortality at 1 year
Leibovici 1995	Prospective study, 1988-1992, Single centre, Israel.	1991 (1:1)	>17 years of age	Age (+/- 5 years), gender, date of hospitalisation (+/- 6 months), department of admission, comorbidity	Yes	Co-morbid disease	4 years	Mortality at 30 days, 6 months and 1 year

BSI = bloodstream infection, COPD = chronic obstructive lung disease, EQ-5D = EuroQol five dimensions questionnaire

Table 3 Proportional difference in mortality with unadjusted risk ratio at reported intervals

Study	30 day	90 day	180 day	365 day
Tauriainen 2017				
BSI	11.1	--	--	18.5
Non BSI	5.1	--	--	9.5
Absolute difference	6	--	--	9
Unadjusted relative risk	2.18 (0.72 to 6.62)	--	--	1.94 (0.85 to 4.42)
Gotland 2016				
BSI	--	--	--	44.6
Non BSI	--	--	--	4.1
Absolute difference	--	--	--	40.5
Unadjusted relative risk	--	--	--	10.94 (10.66 to 11.16)
Nielsen 2015				
BSI	22	30.1	--	41.4
Non BSI	0.2	0.6	--	2.6
Absolute difference	21.8	29.5	--	38.8
Unadjusted relative risk	114.2(90.82 to 143.7)	50.66(44.36 to 57.86)	--	16.19(15.14 to 17.31)
Dalager-Pedersen 2014a				
BSI	4.0	--	--	8.0
Non BSI	1.4	--	--	3.9
Absolute difference	3.6	--	--	4.1
Unadjusted relative risk	2.80(1.71 to 4.59)	--	--	2.05(1.47 to 2.86)
Dalager-Pedersen 2014c				
BSI	--	20.5	--	29.3
Non BSI	--	12.5	--	21.6
Absolute difference	--	8.0	--	7.7
Unadjusted relative risk	--	1.64 (1.53 to 1.76)	--	1.36 (1.29 to 1.43)
Karvellas 2011				
BSI	--	--	--	60
Non BSI	--	--	--	6
Absolute difference	--	--	--	54
Unadjusted relative risk	--	--	--	9.97(5.10 to 19.48)
Leibovici 1995				
BSI	26	--	43	48
Non BSI	7	--	19	27
Absolute difference	19	--	24	21
Unadjusted relative risk	3.73(3.12 to 4.45)	--	2.26(2.04 to 2.51)	1.78(1.6 to 1.94)

Table 4. Studies assessing morbidity at 1 year for BSI and non-BSI matched cohort, and risk assessment.

Study	Morbidity measure	% Morbidity at 1 year bloodstream infection cohort	% Morbidity at 1 year matched cohort	Adjusted risk of morbidity
Dalager-Pedersen 2016	Risk for deterioration in Barthel-20	11	7	1.6 (0.5-4.5)
	Risk for deterioration in EQ-5D-3L	38	31	1.3 (0.8-2.1)
Dalager-Pedersen 2014a	Sick leave	40.2	23.9	1.51(1.34-1.70)
	Disability pension	2.7	2.6	0.99 (0.48-2.02)
Dalager-Pedersen 2014b	Myocardial infarct	0.5	0.6	0.91(0.52-1.60)
	Stroke	0.6	0.7	0.71(0.42-1.20)
Dalager-Pedersen 2014c	Venous thromboembolism	0.5	0.3	1.4(0.8-2.5)
Mejer 2014	Deep vein thrombosis	9.5(7.0–12.9)	2.0(1.8–2.2)	
	Pulmonary embolism	3.0(1.7–5.1)	1.6(1.4–1.8)	
	Risk of venous thromboembolism after exclusion of prior VTE, IVDU or cocaine use			4.5(3.2–6.2)

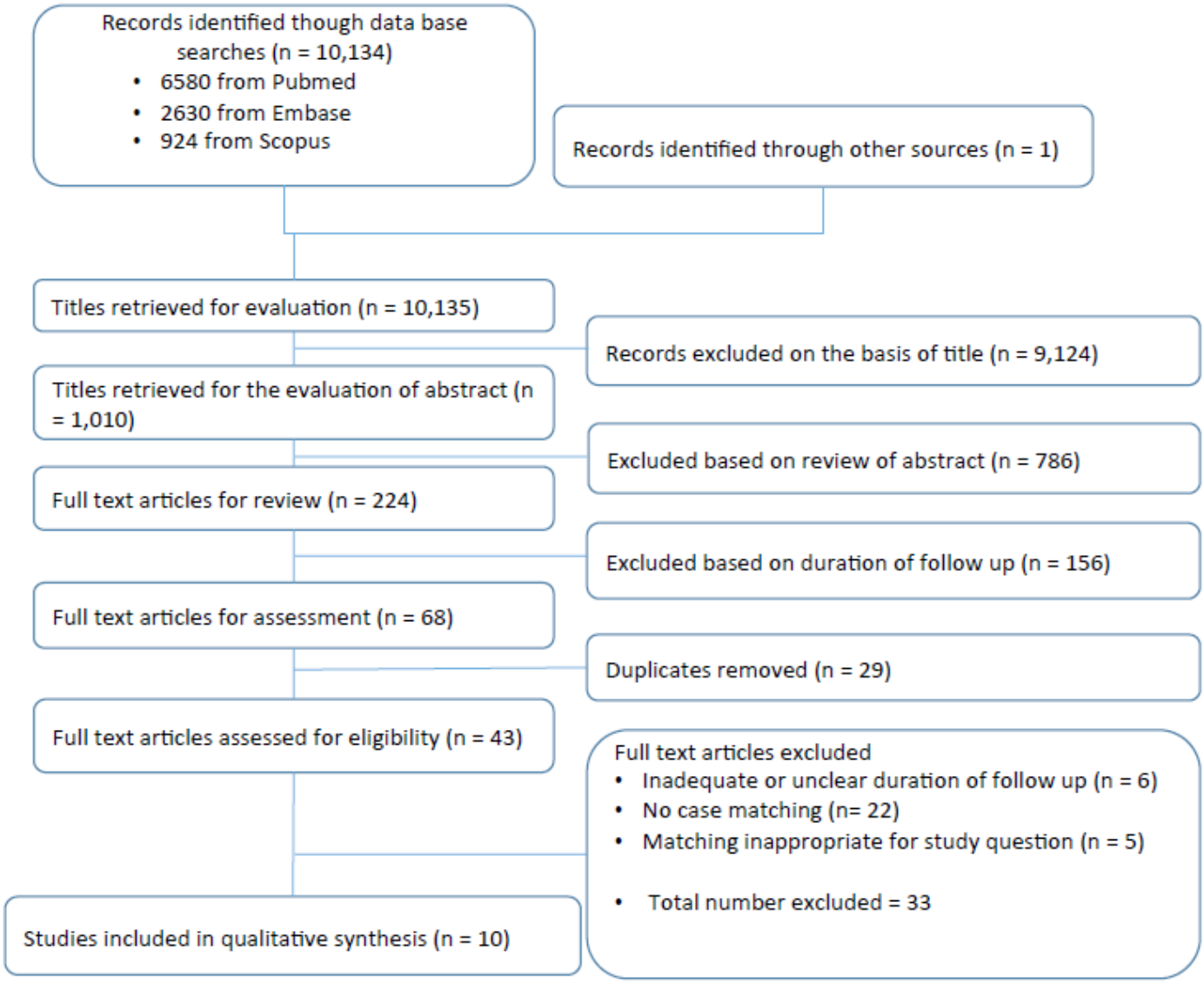

Figure 1

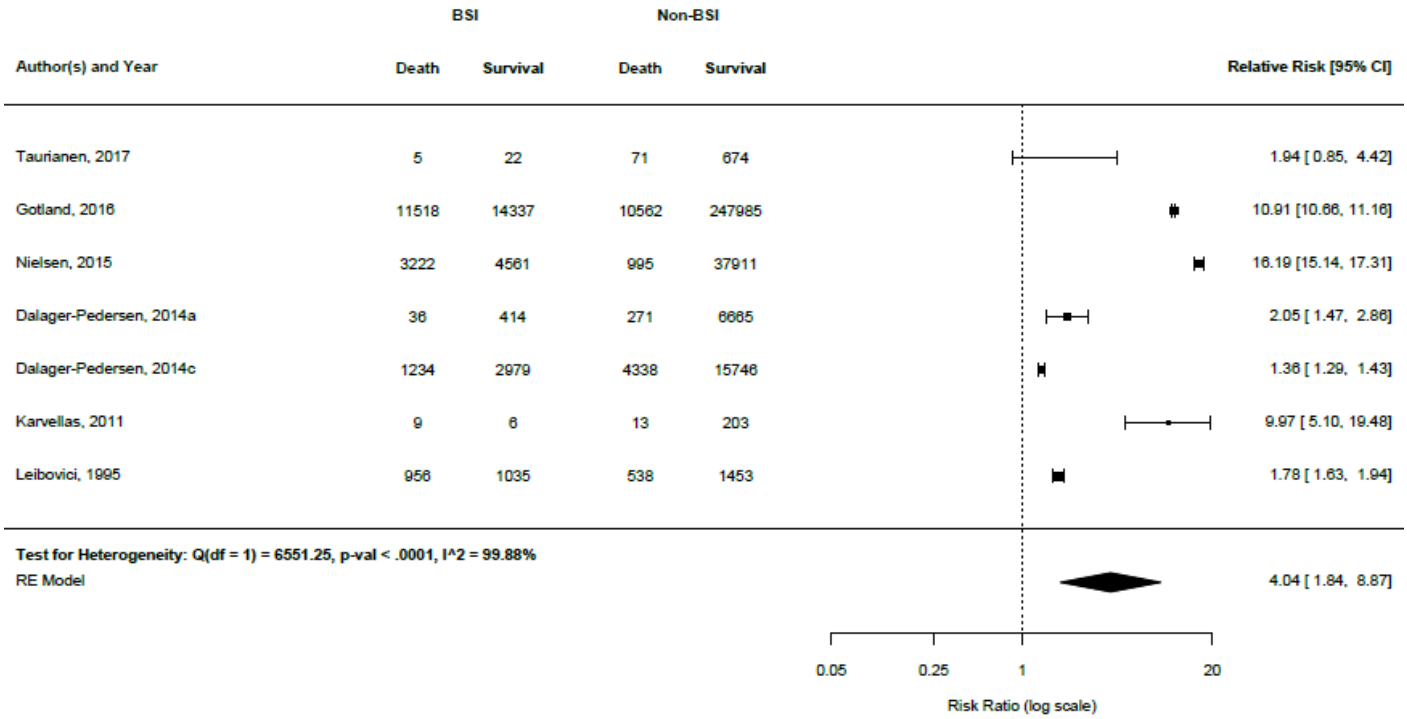

Figure 2

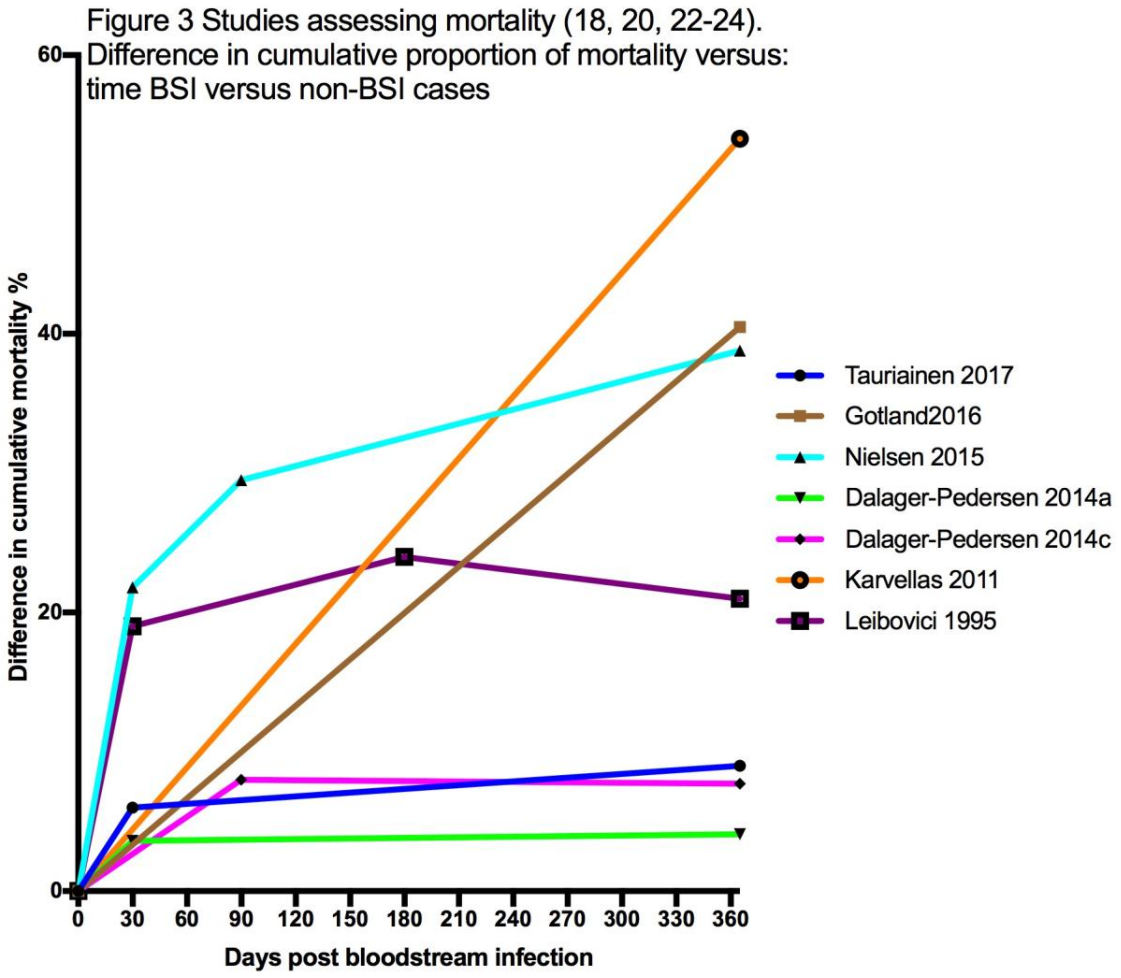

Figure 3